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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/284,180	06/09/99	KIMURA T	20-4546P

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	16

DATE MAILED: 09/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/284,180	Kimura et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-14 and 16-33* is/are pending in the applicat

Of the above, claim(s) *4, 6, 11-14, 16, and 18-33* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5, 7-10, and 17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9 and 10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election of group I, claims 1-3, 5, 7-10 and 17 in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 4, 6, 11-14, 16 and 18-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2, 3 and 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "SEQ ID No. 4 or 5 and/or the base sequence shown in SEQ ID No. 10" in claim 2(e) line 8 is vague and renders the claim indefinite. It is unclear what sequence is intended, SEQ ID No. 4 or 5, or SEQ ID No. 10, or a fusion sequence of SEQ ID No. 4 or 5 and 10 in any order.

The term "stringent conditions" in claims 2, 3 and 7 is vague and renders the claim indefinite. It is unclear what constitutes "stringent conditions" for hybridization between two nucleotide sequences. The specification only give an example of stringent hybridization under 2X SSPE at around 42°C (page 20) but fails to clearly define what "stringent conditions" are. In addition, a washing at 2X SSPE at around 42°C would not be considered a stringent condition in the art. Claims 7-10 depend on claim 7, thus, they are also rejected under 35 U.S.C. 112 second paragraph.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 5, 7-10 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on a gene encoding a protein comprising the amino acid sequence of SEQ ID No. 3 or encoding a protein having one or amino acids deleted, substituted and/or added to SEQ ID No. 3, a DNA which hybridizes with SEQ ID No. 1 or 2 under stringent condition, a gene comprising a DNA that hybridizes with SEQ ID No. 7 under stringent condition and

encodes a protein having a semaphorin domain, a DNA containing the sequence of SEQ ID No. 4 or 5 and/or 10, and a DNA cloned from a human cDNA or genomic DNA library which hybridizes with SEQ ID No. 1, 4, or 10 under stringent conditions, wherein said protein inhibits neurite outgrowth.

The claims encompass any DNA or gene encoding a genus of semaphorin protein variants that have one or more amino acids substituted, deleted or added to SEQ ID No. 3, and any DNA or gene having nucleotide sequence that hybridizes to SEQ ID No. 1, 2, 4, 7 or 10. The specification of the present application only disclosed the nucleotide sequences of SEQ ID Nos. 1 and 2 (rat semaphorin) and the amino acid sequence deduced from SEQ ID No. 2 (SEQ ID No. 3), and the nucleotide sequences of human semaphorin cDNA (SEQ ID Nos. 4, 5, 7 and 10).

The scope of the claim includes numerous structural variants of semaphorin protein, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification only discloses the homologies of the primary amino acid sequences in semaphorin domain among the known semaphorin genes are 20-80% and not necessarily high (specification, page 4, lines 17-20), and suggest that the amino acid residue at position 204 of SEQ ID No. 3 could be essential to the activity of semaphorin protein (specification, page 18, lines 17-22). The specification fails to provide comparison between the protein sequences derived from rat, human and other organisms and fails to provide any other protein sequence or structural features of any semaphorin protein other than the rat semaphorin W having the sequence of SEQ ID No. 3 as disclosed in the present application. The

specification also fails to provide any domain or region within a semaphorin that contributes to any functional characteristic of the semaphorin other than the proposed position 204 of SEQ ID No. 3 and no specific guidance has been provided for any addition, deletion or substitution that would still retain the function of the semaphorin W protein as disclosed in the present application. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of SEQ ID No. 3 is insufficient to describe the genus. This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of all the variants of a semaphorin as claimed in the present invention. Thus it is concluded that the written description requirement is not satisfied for the genus.

Further, in view of the fact that the art does not provide an accepted definition of the term "gene" for semaphorin genes, an elaboration of its characteristics (i.e. sequence) would require both a disclosure of a definition for the term and a characterization of the sequence thereof. The claim under consideration would read on a gene, and such would generally lack an adequate written description in the absence of a specific and particular disclosure of the "gene's" characteristics.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed SEQ ID Nos. 1, 2, 4, 5, 7 and 10, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant

is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. Claims 1-3, 5 and 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA comprising SEQ ID No. 1 or 2 and a DNA encoding a polypeptide sequence of SEQ ID No. 3 that functions to inhibit neurite outgrowth, does not reasonably provide enablement for any isolated DNA encoding a genus of semaphorin polypeptide variants having one or more amino acids deleted, substituted or added to SEQ ID No. 3, any DNA or gene which hybridizes with SEQ ID No. 1, 2, 4, 5, 7 and 10 under stringent condition, any gene comprising a DNA that hybridizes with SEQ ID No. 7 under stringent condition and encodes a protein having a semaphorin domain, and any DNA containing the sequence of SEQ ID No. 4 or 5 and/or 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a gene encoding a protein comprising the amino acid sequence of SEQ ID No. 3 or encoding a protein having one or amino acids deleted, substituted and/or added to SEQ ID No. 3, a DNA which hybridizes with SEQ ID No. 1 or 2 under stringent condition, a gene comprising a DNA that hybridizes with SEQ ID No. 7 under stringent condition and encodes a protein having a semaphorin domain, a DNA containing the sequence of SEQ ID No. 4 or 5 and/or 10, and a DNA cloned from a human cDNA or genomic DNA library which

hybridizes with SEQ ID No. 1, 4, or 10 under stringent conditions, wherein said protein inhibits neurite outgrowth.

The specification of the present application only discloses the nucleotide sequence of SEQ ID No. 1 and 2, the amino acid sequence of SEQ ID No. 3 (a rat semaphorin W protein) and the function of said semaphorin W protein. The scope encompass any semaphorin variants, derived from different organisms including humans, cows, dogs, mice, whales, fish, insects, plants etc., having one or more amino acids substituted, deleted or added to SEQ ID No. 3, and any DNA or gene having nucleotide sequence that hybridizes to SEQ ID No. 1, 2, 4, 7 or 10.

The specification fails to provide adequate guidance for a domain or a region within a semaphorin that contributes to any functional characteristic of the semaphorin having the sequence of SEQ ID No. 3 other than the proposed amino acid residue at position 204 of SEQ ID No. 3. There is no indication of regions or specific amino acids within the semaphorin where mutations or variations would be tolerated without any change of the functional characteristic of the semaphorin and regions where they would not be tolerated other than the proposed amino acid residue at position 204 of SEQ ID No. 3. The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (W) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be

predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Since detailed information regarding the structural and functional requirements of the semaphorin is lacking, it would be unpredictable whether the addition, deletion or substitution of one or more amino acids of SEQ ID No. 3 would still retain the functional characteristic of the amino acid sequence of SEQ ID No. 3.

Further, the nucleotide sequences of SEQ ID Nos. 4, 5, 7 and 10 are partial cDNA sequence of human semaphorin. The specification of the present application fails to provide the full-length open reading frame (ORF) of the human semaphorin and fails to provide adequate guidance and evidence for the function of the protein encoded by said full length ORF of human semaphorin. It is unclear whether a human semaphorin would have the same function as the rat semaphorin W disclosed in the present application. It is also unclear whether any combination of SEQ ID No. 4, 5 and 10 in any order would encode a protein which functions as the rat semaphorin W protein as filed.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that one skilled in the art at the time of the invention would have had to engage in undue experimentation to practice over the full scope of the invention claimed.

The quantity of the experimentation required to practice the invention claimed would include: isolation, purification and characterization of the semaphorin variants having one or more amino acids substituted, deleted or added to SEQ ID No. 3, determination of the function of

said semaphorin variants, determining the structural features and functional domains within the semaphorin that contributes to its function of inhibiting neurite outgrowth, trial and error experimentation to determine what mutations or variations of SEQ ID No. 3 would still retain the functional characteristic of the semaphorin W.

8. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 17 is directed to a pharmaceutical composition comprising the gene or DNA as set forth in claims 1-3, 5 and 7.

In addition to the reasoning set forth above, the term "pharmaceutical composition" implies exhibition of therapeutic effects for a particular disease or a disorder *in vivo*. Claim 17 reads on using a gene or a DNA encoding any semaphorin variant in treating a disease or a disorder of any subject *in vivo*. The specification fails to provide specific guidance and evidence for how to use the gene or DNA set forth above to treat a particular disease or disorder in a subject so as to provide therapeutic effects for said disease or disorder *in vivo*.

The state of the art for gene therapy was unpredictable at the time of the invention. Eck et al., 1996 (X) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the

genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). The instant specification does not provide any *in vivo* working examples. The specification does not teach how to deliver a pharmaceutical composition containing a gene or a DNA to a subject and sufficient amount of the protein is expressed in the targeted site for a sufficient time so as to provide therapeutic effects for a particular disease or disorder *in vivo*.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require a skilled artisan undue experimentation to practice the claimed invention.

The quantity of the experimentation required to practice the invention claimed would include: determination of the function of the protein encoded by the gene or DNA contained in the pharmaceutical composition, determination of the correlation between the encoded proteins and any particular disease or disorder, trial and error experimentation to determine the delivery route of a pharmaceutical composition containing a gene or a DNA as claimed to provide sufficient expression of the encoded protein at the targeted site *in vivo*, and trial and error experimentation to determine whether said encoded protein would provide therapeutic effects for a particular disease or disorder of a subject *in vivo*.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, 5, 7 and 17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hillier et al., 1995 (U2) .

Claims 1, 2, 5 and 7 are drawn to a gene encoding a protein comprising the amino acid sequence of SEQ ID No. 3 or encoding a protein having one or amino acids deleted, substituted and/or added to SEQ ID No. 3, a DNA which hybridizes with SEQ ID No. 1 or 2 under stringent condition or a DNA containing the sequence of SEQ ID No. 4 or 5 and/or 10, and a DNA cloned from a human cDNA or genomic DNA library which hybridizes with SEQ ID No. 1, 4, or 10 under stringent conditions, wherein said protein inhibits neurite outgrowth. Claim 17 is directed to a pharmaceutical composition comprising the gene or DNA as set forth above.

Hillier teaches a human cDNA sequence, EST Accession No. R54387, which is 85.6% identical to base 1127-1551 of SEQ ID No. 3 and said cDNA encodes a protein similar to collapsin that is known to be a member of semaphorin family (specification, page 4, lines 9-11). The sequence of EST Accession No. R54387 would hybridize to SEQ ID No. 1 under stringent conditions. Further, the term "pharmaceutical" in claim 17 is not considered in the 102(b) art

rejection because the use of a composition does not carry weight in a composition claim for art rejection. Thus, claims 1, 2, 5, 7 and 17 are clearly anticipated by Hillier.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohgi et al., 1991 (V2) in view of Hillier et al., 1995 (U2).

Claims 8-10 are directed to an expression plasmid containing the gene or DNA set forth in the 102(b) section, a transformant transformed with said expression plasmid, and a process for producing a recombinant protein by culturing said transformant.

Ohgi teaches construction of a plasmid containing full-length cDNA encoding RNase Rh, transforms yeast cells with said plasmid and produce RNase Rh protein by culturing said transformed yeast cells. Ohgi analyses the secretion of the recombinant RNase Rh protein and assays the RNase activity of said recombinant RNase Rh protein.

Ohgi does not teach using a cDNA encoding a semaphorin for the production of recombinant semaphorin protein.

Hillier teaches a human cDNA sequence, EST Accession No. R54387, which is 85.6% identical to base 1127-1551 of SEQ ID No. 3 and said cDNA encodes a protein similar to collapsin that is known to be a member of semaphorin family (specification, page 4, lines 9-11).

It would have been obvious for one of ordinary skill at the time of the invention to substitute the RNase Rh cDNA with the nucleotide sequence disclosed by Hillier to construct a plasmid expressing a recombinant protein, transform host cells with said construct and produce recombinant protein that is similar to collapsin in order to study the function of said recombinant protein.

Conclusion

No claim is allowed..

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

DEBORAH J.R. CLARK
PRIMARY EXAMINER

Shin-Lin Chen, Ph.D.